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Pulmonary Function in Children Treated for Rhabdomyosarcoma

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Chemotherapy, radiation therapy, and surgical intervention have markedly improved the survival of patients treated for rhabdomyosarcoma. Unfortunately, the therapy may have deleterious effects on the lung. Pulmonary functions tests were obtained from 17 patients treated for rhabdomyosarcoma because of our concern regarding potential pulmonary dysfunction in this group of patients who had received bleomycin, which is known to be associated with lung injury. Mean age at the time of the diagnosis of rhabdomyosarcoma was 10.1 (±7.2) years (range 0.01–23.5 years). The mean age at the time of pulmonary function testing was 17.0 (±7.5) years (range 5.8–34.0 years). Study patients reportedly had no pulmonary symptoms. Approximately 87% of study patients had a restrictive ventilatory impairment on pulmonary function testing as measured by total lung capacity (TLC) values less than the lower limit of normal. Approximately 70% of study patients had carbon monoxide diffusing capacity (D_{LCO}) values less than the lower limit of normal. There were no significant differences in pulmonary function parameters when male study patients were compared to female study patients. There was a statistically significant lower forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio ($P = 0.03$) and percent predicted forced expiratory flow at 25–75% of the FVC (FEF_{25-75}; $P = 0.03$) in the group of patients diagnosed with rhabdomyosarcoma over 8 years of age as compared to those individuals diagnosed under 8 years of age. In addition, there were no statistically significant differences in pulmonary function when the variables of sex and age at diagnosis (as outlined above) were studied in combination.

In summary, we identified a high incidence of restrictive ventilatory abnormalities in a group of individuals (predominantly children) treated for rhabdomyosarcoma as well as a significantly lower FEV_1/FVC ratio and percent predicted FEF_{25-75} in the group of patients diagnosed with the neoplasm over 8 years of age. Individuals caring for such patients are encouraged to obtain pre- and sequential posttreatment pulmonary function tests.

Key words: pulmonary function, children, rhabdomyosarcoma

INTRODUCTION

Rhabdomyosarcoma is the most common soft tissue sarcoma in children less than 15 years of age [1]. Treatment regimens including chemotherapy, radiation therapy, and surgical intervention have markedly improved survival [1]. Unfortunately, the therapy may have deleterious effects on the lung [1]. There have been no previous reports on pulmonary function in patients treated for rhabdomyosarcoma and, thus, the pulmonary outcome of these individuals remains unknown. Pulmonary function tests (PFTs) were obtained in a group of individuals (predominantly children) treated for rhabdomyosarcoma because of our concern regarding potential lung dysfunction in this group of patients who had received bleomycin, which is known to be associated with lung injury.

MATERIALS AND METHODS

One hundred thirty-one individuals diagnosed with rhabdomyosarcoma between 1975 and 1989 were treated under the "T_6" treatment protocol (Fig. 1) at Memorial Sloan-Kettering Cancer Center. Sixty-one of these individuals are alive. No deaths were due to lung disease. Seventeen of the 61 survivors had pulmonary function data available for study. The induction phase consisted of three parts as shown in Figure 1 and as outlined by Ghavimi et al. [2]. Patients treated in the earlier years under this protocol received cyclophosphamide (1,200 mg/m^2 or 40 mg/kg intravenously [IV]) concurrent with BCNU (90 mg/m^2 or 3 mg/kg IV) as shown in Figure 1,

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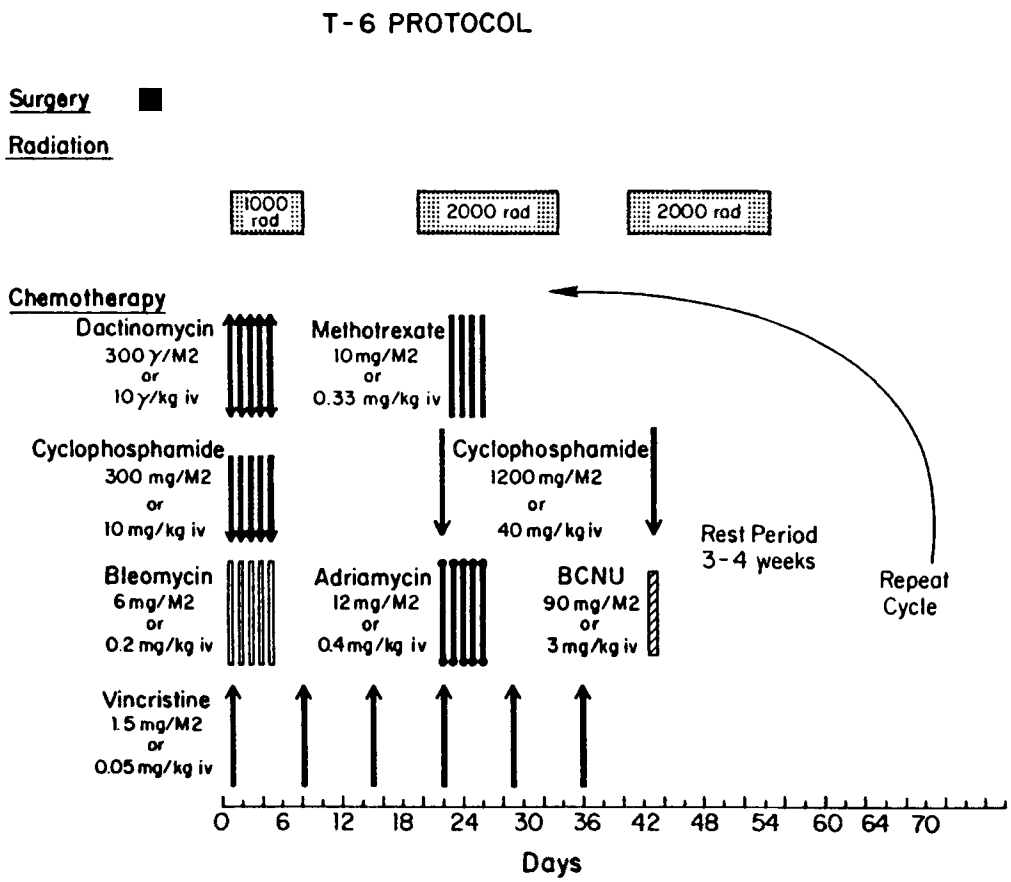

Fig. 1. T_6 induction therapy. Printed with permission from *Journal of the National Cancer Institute* [2].

followed by a 3–4-week rest period [2]. Subsequently, this phase was omitted due to thrombocytopenia. Chemotherapy doses were modified according to side effects as previously outlined [2]. The duration of therapy under the T_6 protocol was approximately 12–14 months. Fifteen of 17 study patients received maintenance therapy as outlined for the T_6 protocol and two study patients received "T_2" maintenance therapy [2,3]. T_2 maintenance therapy consisted of T_2 induction therapy minus one course of Adriamycin. Two of the study patients received additional cytoreductive therapy associated with bone marrow transplant (BMT).

We studied PFTs from 17 patients treated under this protocol who had the studies performed as part of their routine long-term follow-up between June, 1991 and June, 1993. Mean age at the time of the diagnosis of rhabdomyosarcoma was 10.1 (±7.2) years (range 0.01–23.5 years). Three patients were over the age of 18 at the time of diagnosis (18.44–23.52 years). The mean age at the time of PFT was 17.0 (±7.5) years (range 5.8–34.0 years). One study patient had two PFTs, the better test was selected. Of the two patients in this study who had BMTs, the PFT in one of the patients was after BMT and in the second patient after the first of two BMTs. Study patients were not systematically questioned with regard to a past history of allergies or pulmonary disease. However, no overt pulmonary symptoms were reported. Furthermore, none of the study patients had serious pulmonary or other infectious episodes during their therapy that could have resulted in residual damage.

Pulmonary function testing was performed on Collins DSII or GS systems (Collins, Inc., Braintree, MA) in accordance with American Thoracic Society protocols in the pulmonary function laboratory at Memorial Sloan-Kettering Cancer Center. Pulmonary function parameters presented in this paper include the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio, forced expiratory flow at 25–75% of the FVC (FEF_{25-75}), total lung capacity (TLC), and carbon monoxide diffusing capacity (D_{LCO}). Values for FVC, FEV_1, FEF_{25-75}, TLC, and D_{LCO} are expressed as mean percent predicted values for the study group. Predicted values for children [4,5] and adults [6–8] were calculated from published equations. Predicted equations for vital capacity as published by Weng and Levison [4] were used for the FVC for the children in this study. The FEV_1/FVC ratio is expressed as a percent of the absolute value of the FEV_1 divided by the absolute value of the FVC.

TABLE I. Data on Study Patients

Patient	FVC (liters)	FEV_1 (liters)	FEF_{25-75} (liters/sec)	FEV_1/FVC (%)	TLC (liters)	D_{LCO} (ml/min/mm Hg) (corr. Hb)	Time from diagnosis to PFT (years)	Age at diagnosis (years)	Age at PFT (years)
1[a]	1.040	0.99	1.17	95.2	1.530	8.57	2.16	3.64	5.80
2	1.745	1.58		90.5	2.325	16.39	6.53	3.76	10.28
3[b]	2.530	2.47	4.16	97.6	2.880	16.46	10.19	4.68	14.87
4	3.460	3.19	4.48	92.2	3.920	26.33	6.83	8.62	15.45
5	4.640	4.17	5.30	89.9	5.650	29.94	4.28	18.44	22.72
6	2.210	2.20	2.94	99.5	3.260	20.54	4.25	12.42	16.67
7	5.580	4.33	3.50	77.6	6.400	32.26	7.09	11.03	18.12
8	2.290	2.17	3.15	94.8	2.580	14.76	5.16	7.91	13.07
9	1.690	1.66	2.31	98.2		19.78	4.29	8.85	13.14
10[c]	3.660	3.20	3.75	87.4	5.550	29.34	3.03	23.52	26.55
11	1.900	1.79	2.64	94.2	2.590	13.62	8.68	2.09	10.76
12	1.320	1.28	2.39	97.0	1.760	9.5	11.99	0.01	12.00
13	1.030	1.00	1.63	97.1		7.12	4.86	2.62	7.48
14[b]	4.370	4.23	6.17	96.8	5.990	25.85	14.42	7.21	21.63
15[a,d]	4.580	3.91	4.22	85.4	5.200	30.47	2.59	17.8	20.39
16	4.210	3.65	4.21	86.7	5.140	23.5	8.76	17.52	26.28
17	3.720	3.15	3.58	84.7	4.930	18.09	13.04	20.98	34.02

[a]Received BMT (patient 1: PFT after BMT; patient 15: PFT after one of two BMTs).
[b]Received carmustine (patient 3: 90 units; patient 14: 150 units).
[c]Received chest surgery (metastases resected on diaphragmatic surface) and 5,400 cGy radiation therapy (RT) to anterior chest wall.
[d]Received RT & surgery around right upper lobe of lung and right axilla.

Abnormal values were those below the fifth percentile [9]. Physiologic techniques for assessment of pulmonary function are described by Cotes and Leathart [10].

Analyses were performed using the *Clinfo*[1] and SAS (SAS Institute, Cary, NC) data management system. Descriptive analyses are presented for the group data. Two-way analysis of variance (ANOVA) was performed to compare the pulmonary function of male study patients to those of female study patients, to compare pulmonary function of those individuals diagnosed with rhabdomyosarcoma less than 8 years of age to those patients diagnosed over 8 years of age, as well as sex and age in combination. $P < 0.05$ was considered statistically significant.

RESULTS

Table I outlines the specific PFT results as well as additional data on the individual study patients. The mean percent predicted FVC for the study group was 80.0% (±21.1%) (Table II). Eleven of 17 (64.7%) patients had abnormal FVC values. The group mean FEV_1 values was 106.6% (±32.3%) (Table II). Five of 17 (29.4%) patients had FEV_1 values less than the lower limit of normal. The group mean FEV_1/FVC value was 92.0% (±6.0%) (Table II). None of the study patients had abnormal FEV_1/FVC ratios. The group mean FEF_{25-75} value was 93.6% (±22.7%) (Table II). Four of 16 (25.0%; data was unavailable for one patient) patients had abnormal FEF_{25-75} values. The group mean TLC was 80.0% (±15.5%) of the predicted value (Table II). Thirteen of 15 patients (86.7%; TLC data were unavailable for two patients) had TLC values less than the lower limit of normal. The mean D_{LCO} value for the study group was 75.6% (±18.5%) of the predicted value (Table II). Twelve of 17 (70.6%) study patients had D_{LCO} values less than the lower limit of normal. There were no significant differences in the pulmonary function parameters when male study patients were compared to female study patients (Table III). Listed in Table IV are the pulmonary function parameters of patients who were diagnosed with rhabdomyosarcoma under 8 years of age as compared to individuals diagnosed with the neoplasm after 8 years of age. There was a statistically significant lower FEV_1/FVC ratio (89.1% ± 6.9%; $P = 0.03$) as well as percent predicted

TABLE II. Mean Pulmonary Function Values (± 1 S.D.) and Percent of Patients With Abnormal Pulmonary Function Values

	N	Mean (± 1 SD)	% of patients with abnormal values
FVC[a]	17	80.0 (±21.1)	64.7
FEV_1[a]	17	106.6 (±32.3)	29.4
$FEV_1/FVC\%$	17	92.0 (±6.0)	0.0
FEF_{25-75}[a]	16	93.6 (±22.7)	25.0
TLC[a]	15	80.0 (±15.5)	86.7
D_{LCO}[a]	17	75.6 (±18.5)	70.6

[a]Mean values expressed as percent predicted.

[1]*Clinfo* is a registered trademark of the U.S. Department of Health and Human Resources.

TABLE III. Pulmonary Function Values of Male Study Patients vs. Female Study Patients

	Males	N	Females	N	*P*
FVC[a]	85.4 (±12.3)	9	74.0 (±27.7)	8	NS
FEV_1[a]	108.4 (±22.5)	9	104.5 (±42.4)	8	NS
FEV_1/FVC%	90.7 (±6.4)	9	93.6 (±5.6)	8	NS
FEF_{25-75}[a]	101.0 (±27.6)	8	86.3 (±15.0)	8	NS
TLC[a]	83.7 (±10.3)	8	75.9 (±20.0)	7	NS
D_{LCO}[a]	71.1 (±15.9)	9	80.6 (±21.0)	8	NS

[a]Mean values expressed as percent predicted.

TABLE IV. Pulmonary Function Values of Study Patients Diagnosed With Rhabdomyosarcoma Under 8 Years of Age vs. Those Individuals Over 8 Years of Age

	<8 years old	N	>8 years old	N	*P*
FVC[a]	75.9 (±15.2)	8	83.7 (±25.7)	9	NS
FEV_1[a]	119.5 (±37.8)	8	95.0 (±22.7)	9	NS
FEV_1/FVC%	95.4 (±2.3)	8	89.1 (±6.9)	9	0.03
FEF_{25-75}[a]	104.9 (±20.4)	7	84.8 (±21.4)	9	0.03
TLC[a]	78.3 (±18.0)	7	81.5 (±14.1)	8	NS
D_{LCO}[a]	75.6 (±20.7)	8	75.6 (17.6)	9	NS

[a]Mean values expressed as percent predicted.

FEF_{25-75} (84.8% ± 21.4%) in the group of patients diagnosed with rhabdomyosarcoma over 8 years of age as compared to those individuals diagnosed under 8 years of age. There were no statistically significant differences in the other pulmonary function parameters assessed when similar comparisons were made (Table IV). Furthermore, there were no statistically significant differences in pulmonary function when both the variables of sex and age at diagnosis (as outlined above) were studied in combination (data not shown).

DISCUSSION

We found a high incidence of pulmonary function abnormalities, specifically restrictive ventilatory abnormalities, in this group of asymptomatic individuals (predominantly children) treated for rhabdomyosarcoma. Approximately 87% of the patients in this study had diminished TLC measurements and approximately 71% of study patients had abnormalities in their diffusing capacity. No individual study patient had evidence of obstructive lung disease as evidenced by diminutions of the FEV_1/FVC ratio. However, approximately 65% and 29% of study patients had abnormalities of the FVC and FEV_1, respectively. These diminutions may be reflective of their restrictive ventilatory abnormalities in view of normal FEV_1/FVC ratios in the study patients. Decreases in the FVC and FEV_1 are frequently seen in patients with restrictive ventilatory impairment. There were no statistically significant differences when male study patients were compared to female study patients. However, when patients who were diagnosed with rhabdomyosarcoma under 8 years of age were compared to those individuals diagnosed with rhabdomyosarcoma over 8 years old (the majority of alveolar development occurs in the first 8 years of life), there was a statistically significantly lower FEV_1/FVC ratio and percent predicted FEF_{25-75} in the group of patients diagnosed with rhabdomyosarcoma over 8 years of age. It is, perhaps, possible that the differing ages at time of PFT and the different predicted equations for children and for adults could, in part, account for the statistically significant differences. Furthermore, there were no statistically significant differences when sex and age at diagnosis (as outlined above) were studied in combination.

The nature of the restrictive ventilatory changes in the study patients may be multifactorial. That is, the affected individuals may have small lung volumes and/or interstitial lung disease. Our data do not distinguish between these two pathologic processes. D_{LCO}/V_A data may have helped to make this distinction, however, there were insufficient data available from this study population. Nonetheless, the fact that approximately 71% of the study population had abnormalities of the D_{LCO} suggests that an error of gas transfer may be present. Interestingly, the age at the time of treatment may have contributed to a patient's pulmonary outcome. Approximately, half of the patients in this study were less than 8 years of age at the time of diagnosis, and, hence, when therapy was begun. This is important because the bulk of alveolar development occurs within the first 8 years of life [11]. Subsequent alveolar growth occurs by an increase in volume or size [12]. Hence, insults to the lung at important stages of development may blunt its growth. There are also other considerations in a growing child; i.e., irradiation of cartilage and bone can arrest thoracic growth and, thus, secondarily limit lung growth [12]. Furthermore, as in adult oncology patients, the lung may sustain direct injury from the cytoreductive therapies [12,13]. Thus, pulmonary impairment in children can result from either direct injury to the lung, suboptimal growth of the lung, or a combination of suboptimal thoracic growth with secondary limitations on lung growth. Compensatory hyperplasia and hypertrophy may help to preserve pulmonary function in some patients [14].

Patients in this treatment protocol received multidrug regimens including dactinomycin, cyclophosphamide, Adriamycin, vincristine, bleomycin, and methotrexate. Two patients also received carmustine, a well-known pulmonary toxin [13]. Bleomycin-induced lung injury is well documented, occurring with an incidence of less than 2–40% in different series, the higher incidence occurring with higher doses of the drug [13,15]. Restrictive pulmonary impairment in adults is known to be a particular problem, occurring with an incidence of 35% in patients

receiving at least 450 units of the drug [16]. In general, patients in this study received less than 200 units of bleomycin. It may be that the "threshold" dose of bleomycin associated with pulmonary toxicity in children is different from that in adults, particularly when given as part of a multidrug treatment regimen. Cyclophosphamide and methotrexate have also been associated with pulmonary toxicity but to a lesser degree than occurs with bleomycin [15]. As mentioned above, confounding the issue of chemotherapy-associated pulmonary toxicity are multidrug treatment regimens such as those received by our study patients. Combined drug therapies can enhance pulmonary toxicity [13]. It may be that chemotherapeutic agents not commonly associated with pneumonopathy are toxic to the lung when given as part of multidrug regimens.

Radiation injury to the lung is well recognized [17], and may have a synergistic toxicity when combined with certain chemotherapeutic agents [13]. Only two study patients received radiation therapy to or near the chest, thus, as a group, radiation-associated pulmonary impairment was probably not a major contributing factor to pneumonopathy in this study population.

Underlying pneumonopathy is a risk factor for the development of further lung disease in oncology patients [13]. The contribution of baseline pulmonary impairment to subsequent pulmonary impairment cannot be ascertained in this study as pretreatment PFTs were not available for a comparison analysis. Nonetheless, a restrictive ventilatory impairment predating the presentation of the tumor and its therapy would be unlikely, as restrictive pneumonopathy is rare in children. The group of patients diagnosed with rhabdomyosarcoma over 8 years of age had a significantly lower FEV_1/FVC ratio and percent predicted FEF_{25-75} than the group of patients diagnosed with rhabdomyosarcoma younger than 8 years of age, implying airflow obstruction (Table III). The reason for this is unclear. Approximately 10% of individuals in the general population have obstructive lung disease. It is conceivable that more of the older patients at the time of diagnosis had FEV_1/FVC ratios and FEF_{25-75} values at the time of PFT closer to the lower limit of normal compared to patients diagnosed with rhabdomyosarcoma at a younger age, thus skewing the data. Additionally, pulmonary function declines with age [10]. The effects of aging may be contributory, perhaps, accelerated by previous cytoreductive regimens received by the study patients.

Clearly, the site of tumor presentation may affect pulmonary function. Approximately 7% of patients with rhabdomyosarcoma present with a neoplasm on the trunk [1]. Only one patient in the study had a chest wall presentation of their rhabdomyosarcoma and pulmonary metastases. Two patients had chest surgery (one patient presented with a forearm tumor and received chest surgery/irradiation of the right axilla and around the right upper lobe of the lung). Needless to say, chest surgery and irradiation could have contributed to the pulmonary dysfunction seen in these two patients. In addition, two patients in this study had PFTs after BMT. The development of pneumonopathy is known after BMT [18,19]. However, it is difficult to determine the degree of pulmonary impairment associated with BMT in these two individuals. In general, the PFTs of the BMT recipients were not considerably worse than those of the other study patients.

The major limitation of the present study is the small number of patients having had PFTs during the study period. There may be some bias in the data because patients with problems may be more likely to be seen in clinic during the study period. These data are also limited by the lack of pretreatment and subsequent longitudinal posttreatment pulmonary function data. In addition, the study population is a very heterogeneous group of individuals (e.g., the site of the tumor and specific therapies). Furthermore, pulmonary function measurements were obtained over a wide age range. Hence, it is perhaps possible that the use of different predicted pulmonary function equations for children and for adults may induce some systematic difference in the percent predicted measurements across age. It does not, however, appear that those study patients with the worst PFTs were those treated more recently and are still unable to perform because of generalized deconditioning. Despite these problems, the importance of this study is that it is the first report of pulmonary function in children treated for rhabdomyosarcoma. Longitudinal studies in larger patient populations would provide clear information on the incidence and severity of lung disease in this patient population.

In summary, we identified a high incidence of restrictive ventilatory abnormalities in a group of individuals (predominantly children) treated for rhabdomyosarcoma as well as a significantly lower mean FEV_1/FVC ratio and percent predicted FEF_{25-75} in the group of patients diagnosed with the neoplasm over 8 years of age. Individuals caring for such patients are encouraged to obtain pre- and sequential posttreatment PFTs.

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